General

Guideline Title

Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 44 p. (Technology appraisal guidance; no. 292).

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 3, 2016 – Aripiprazole (Abilify, Abilify Maintena, Aristada) : The U.S. Food and Drug Administration (FDA) is warning that compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with the use of the antipsychotic drug aripiprazole (Abilify, Abilify Maintena, Aristada, and generics). These uncontrollable urges were reported to have stopped when the medicine was discontinued or the dose was reduced. These impulse-control problems are rare, but they may result in harm to the patient and others if not recognized.

Recommendations

Major Recommendations

Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Bipolar I disorder

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Pediatrics

Psychiatry

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder

Target Population

Adolescents aged 13 and older with acute manic or mixed episodes associated with bipolar I disorder

Interventions and Practices Considered

Aripiprazole

Major Outcomes Considered

- Clinical effectiveness:
  - Response rate
  - Range and severity of symptoms of mania and depression
  - Recurrence of manic episodes

    - Body mass index
    - Health-related quality-of-life
    - Adverse effects of treatment
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this technology appraisal was prepared by School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Systematic Reviews for Clinical Efficacy

Two systematic reviews were performed for the assessment of clinical effectiveness in the manufacturer's submission (MS). The objective of the first systematic review was to identify all relevant clinical information available for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents with aripiprazole. The review was based on the search and inclusion strategy of a previous systematic review (commissioned by NICE in 2005) which did not identify any relevant randomised controlled trial (RCT) or non-RCT evidence for aripiprazole in children and adolescents with bipolar I disorder.

The second systematic review was designed with the objective of identifying all relevant clinical information available for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents with the following comparators:

- Risperidone
- Quetiapine
- Olanzapine
- Combination of any of the above with lithium or valproate

This review was also based on the same search and inclusion strategy as the NICE 2005 review, and identified three randomised controlled trials that examined the use of antipsychotics in the treatment of mania in children and adolescents. However, only the results from one trial were included in this update.

Of the two other excluded studies, one was an open label trial including some bipolar II patients, and one was a semi-RCT which also included bipolar II patients. For the long term management of children and adolescents with bipolar disorder, the only study identified by the previous systematic review was excluded not only because it examined lithium, but also because it included a mixture of bipolar I and II patients.

It was not clear from the MS why the searches for both reviews were limited up to January 2012 which makes the evidence generated from their searches one year out of date and therefore clarification was requested from the manufacturers. The manufacturers did update the searches on February 4th 2013 in response to the clarification questions raised by the ERG. The manufacturers stated that rather than repeating their searches a non-systematic approach was used to find further studies since January 2012 due to time constraints. Only PubMed, Google Scholar and ClinicalTrials.gov were searched by the manufacturers but EMBASE and Cochrane Library were not searched. Four RCTs and three non-RCTs were identified.

The ERG repeated and updated the searches until January 2013 using the systematic approach in the MS. Database searches were repeated and updated by using strategies provided in the MS.

The searches for RCT evidence regarding the intervention (aripiprazole) and the comparators (risperidone, quetiapine, olanzapine, or in

combination with lithium or valproate) were considered comprehensive. However in the searches for non-RCT evidence, the use of the heading "Epidemiologic study characteristics" in the RCT search filter was too restrictive and not adequate to capture non-RCT evidence in this search strategy. This search strategy for non-RCT evidence was not clearly justified in the MS or clarification response from the manufacturer.

Justification for the omission of adverse events searches were not provided in the MS or explained in the clarification response. As a result, the ERG carried out supplementary searches in MEDLINE and EMBASE for adverse event using previously published methods. Further details of the supplementary searches are provided in Appendix 1 of the ERG report.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria used in the selection of evidence for the systematic review of clinical effectiveness were presented in the MS. The MS reports that each review was performed independently by 2 reviewers, who then came to a consensus on the results.

Inclusion Criteria

- Patients with manic or mixed episodes of bipolar I disorder
- Patients aged <18 years
- At least 1 of the interventions studied must be aripiprazole
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study
- RCT
- Non-RCT that still evaluates the effectiveness of interventions (acceptable study designs: prospective cohort study, retrospective chart/database review)
- English language

Exclusion Criteria

- Cross-sectional or retrospective studies

The inclusion criteria for the review appeared reasonable and relevant to the decision problem. See Table 4 in the ERG report for detailed inclusion/exclusion criteria for the main study and the additional RCT.

Economic Evaluation

ERG Comment on Manufacturer's Review of Cost-Effectiveness Evidence

The manufacturer did not identify any relevant economic evaluations. The manufacturer's search strategy was based on a previously published systematic review in order to identify all relevant cost-effectiveness information available for the treatment of acute manic and mixed episodes in bipolar I disorder in children and adolescents.

The MS reports that 6,694 records were found. As with the systematic review for clinical efficacy, searches were limited to January 2012. The ERG was able to repeat and update the database searches until January 2013. A total of 7,056 records were retrieved, of which 955 were in 2012 which represents a significant number of records that were missed by the manufacturers searches that were conducted up to January 2012. Whilst the quality of life terms were comprehensive, the cost filter was somewhat restrictive, and the ERG recommends the use of a sensitive filter such as Scottish Intercollegiate Guidelines Network (SIGN). The ERG does not believe that any additional relevant studies were missed by the manufacturer's cost-effectiveness review.

Number of Source Documents

Clinical Effectiveness

- One randomised controlled trial (RCT) was included in the review
- One additional RCT was included for meta-analysis
- Five studies were included for network meta-analysis

Cost-Effectiveness

- No relevant economic evaluations were identified
- The manufacturer submitted an economic model

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this technology appraisal was prepared by School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Describe and Critique the Manufacturer's Approach to Validity Assessment

Trials NCT00110461 and NCT00116259 employ the Young Mania Rating Scale (YMRS) as the primary outcome measure. The manufacturer's submission (MS) states that the YMRS scale is widely accepted and commonly used for measuring manic symptoms in clinical trials with children and adolescents with juvenile bipolar disorder. The clinical advisors to the ERG have stated that the use of the YMRS is appropriate for evaluating efficacy of antipsychotic medication. The ERG is satisfied that the outcome measures investigated in the MS ensure that the included studies and assessment undertaken by the manufacturers is internally valid.

Quality assessment was undertaken by the manufacturer using the suggested format in the NICE specification for manufacturer/sponsor submission of evidence template in summary form for both trials and in fuller detail for trial NCT0011046121. The quality assessment for trial NCT0011046121 is presented in Table 8 of the ERG report.

Statistical Analyses

The statistical analysis for trial NCT00110461 for the primary endpoint is described as an overall F-test for mean change from baseline in YMRS total score at a significance level of 0.05 (two-tailed) for the aripiprazole 10 mg, aripiprazole 30 mg and placebo groups. The differences between groups (aripiprazole 10 mg versus placebo and aripiprazole 30 mg versus placebo) were investigated using a two-tailed test at 5% significance.

Changes in scores from baseline were analysed using analysis of covariance (ANCOVA) with treatment as a factor and baseline score as a covariate at each time point. Least squares (LS) means were used for the treatment comparisons. Two-tailed Student t-tests were used to test differences between the LS means within the ANCOVA model. The proportion of responders was analysed using chi-squared tests. The proportion of patients with clinically significant weight gain (≥7% increase from baseline) was tested using the Fisher exact test.

Meta-Analysis: Aripiprazole Versus Placebo

A meta-analysis of NCT00110461 (pooled 10 to 30 mg dose) and NCT00116259 (20 mg dose aripiprazole) was performed. Results were not provided as forest plots for the meta-analysis. The manufacturers concluded from their analysis that:

- The meta-analysis found aripiprazole to still be statistically significantly superior to placebo in inducing symptomatic response (as measured by >50% change in YMRS score) at weeks 1, 2 and 4, but not at week 3.
- The meta-analysis found aripiprazole to be associated with a statistically significant higher rate of extrapyramidal symptoms than placebo, but not of somnolence.

- However, the small size of study NCT00116259 and the different patient population from the pivotal aripiprazole study (includes bipolar II disorders and restricted to patients with attention deficit hyperactivity disorder [ADHD]) means that the results are of limited use.

See Section 4 in the ERG report for additional information on clinical effectiveness analysis including network meta-analysis.

Economic Evaluation

Summary and Critique of Manufacturer's Submitted Economic Evaluation by the ERG

NICE Reference Case Checklist

See Table 50 of the ERG report for information regarding consistency of the manufacturer's economic evaluation with the NICE reference case checklist.

Model Structure

The manufacturer provided a *de novo* model-based economic evaluation constructed in Microsoft Excel and based upon a cohort Markov model. In addition to an absorbing death state, the manufacturers modelled 22 different health states, divided into four distinct groups. Three of these groups related to antipsychotic treatment lines (first-, second- and third-line) and were identical in structure: each contained an acute phase (consisting of three separate health states based on elapsed time), a sub-acute phase, and a maintenance phase (consisting of two separate health states based on whether or not the patient was assumed to be on treatment). The fourth group consisted of four separate health states which modelled therapy resistance for patients who had not responded to the three lines of antipsychotic treatment.

A schematic of the model is shown in Figure 2 of the ERG report. The modelling of adverse events was included within the treatment-related health states. Patients were modelled as receiving in-hospital treatment for all of the health states within the acute and sub-acute phases, as well as the "Therapy Resistance Hospitalised" state. Patients could die at any point in the model.

All patients enter the model at the start of the first treatment line (in the health state "Acute 1st line Week 1"). Patients move through the treatment lines if either they discontinue drug use before response (i.e., during the acute phase) or if they relapse before discharge from hospital (i.e., during the sub-acute phase). If patients relapse within the maintenance phase they remain on the same treatment line to which they responded. The "Therapy Resistance Phase" is essentially the fourth and final treatment line, where treatment is assumed to be lithium. Quality-adjusted life years (QALYs) are accrued as time spent in each health state, with different utility values for the acute, sub-acute and maintenance phases (the lowest utility values are for the acute phase and the highest are for the maintenance phase). The main driver of costs is time spent as an inpatient (in either the acute or sub-acute phases). Treatment effectiveness was reflected by the time spent within each model phase (acute, sub-acute or maintenance).

The Markov model used a cycle length of one week, to reflect the timing of assessments in the pivotal trial for aripiprazole. The ERG believes that weekly Markov cycles are appropriate because the first three weeks of acute treatment are the main drivers of cost-effectiveness results. The option for half-cycle correction was included in the model but was not used in the base case results presented in the MS. Including a half-cycle correction slightly reduces the total costs and total QALYs for each strategy, but does not alter the conclusions of the economic evaluation.

See Section 5 in the ERG report for more information on the cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites "consultee" and "commentator" organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal

documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an "assessment report". Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the "appraisal consultation document" (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the "final appraisal determination" (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on Cost-Effectiveness

Availability and Nature of Evidence

The Committee considered the manufacturer's economic model and the Evidence Review Group's (ERG's) critique and exploratory analysis. It noted that the ERG considered the manufacturer's model to be transparent, robust, and well structured. The Committee agreed that the model structure was appropriate.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was aware that the manufacturer's probabilistic sensitivity analyses suggested that there was uncertainty surrounding the incremental cost-effectiveness ratios (ICERs) and it understood that this may be a result of the lack of statistically significant differences in response rates obtained from the network meta-analysis for the four antipsychotics.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values/Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

Not applicable as the Committee had no concerns about the health-related quality-of-life data used in the manufacturer's economic model.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

Not applicable to this appraisal.

What Are the Key Drivers of Cost-Effectiveness?

The Committee was aware that the main parameters that influenced the results were the rates of response applied during the treatment phase. The

Committee noted that a higher response rate during the treatment phase resulted in people leaving hospital earlier, which had both cost and health-related quality-of-life benefits.

Most Likely Cost-Effectiveness Estimate (Given as an ICER)

The Committee noted that the pathway in which aripiprazole was positioned second dominated all of the other strategies. The Committee also noted that the ranges of costs and quality-adjusted life years (QALYs) (in the base case, costs ranged from £74,133 to £75,066, and QALYs ranged from 2.516 to 2.525) across the strategies were similar. Results from the sensitivity analyses demonstrated that each of the strategies was dominated by every other strategy in at least some of the probabilistic iterations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD) and were provided with the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, one randomised controlled trial was the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder

Potential Harms

The summary of product characteristics lists the following adverse reactions specific to adolescents treated with aripiprazole: very common reactions (10% or more) were somnolence (23.0%), extrapyramidal disorder (18.4%), akathisia (16.0%) and fatigue (11.8%); and common reactions (between 1% and 10%) were upper abdominal pain, increased heart rate, increased weight, increased appetite, muscle twitching and dyskinesia. The following undesirable effects had a possible dose–response relationship: extrapyramidal disorder (incidences were: 10 mg dose 9.1%, 30 mg dose 28.8%, placebo 1.7%) and akathisia (incidences were: 10 mg dose 12.1%, 30 mg dose 20.3%, placebo 1.7%). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring.

For full details of adverse reactions and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/ .

Qualifying Statements

Qualifying Statements

- This guidance represents the views of National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment "as an option", the NHS must make sure it is available within the period set out in the paragraph above. This means that, if an adolescent has moderate to severe manic episodes in bipolar I disorder and the doctor responsible for their care thinks that aripiprazole is the right treatment, it should be available for use, in line with NICE's recommendations.
- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE Web site (http://guidance.nice.org.uk/TA292).
    - A costing statement explaining the resource impact of this guidance.

Implementation Tools

Foreign Language Translations

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 44 p. (Technology appraisal guidance; no. 292).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Jul

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder. Technology Assessment Report. Sheffield (UK): School of Health and Related Research (ScHARR), The University of Sheffield. 2013 Mar 13. 156 p. Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Care Excellence (NICE) Web site .
- Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 4 p. (Technology appraisal guidance; no. 292). Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Aripiprazole for manic episodes in adolescents with bipolar I disorder. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 6 p. (Technology appraisal guidance; no. 292). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Care Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on October 31, 2013. This summary was updated by ECRI Institute on May 31, 2016 following the U.S. Food and Drug Administration advisory on Aripiprazole (Abilify, Abilify Maintena, Aristada).

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